REMARKS

Claims 37, 45, 48, 53, 54, 72, and 75 to 78 and new Claim 80 are present for purposes of prosecution.

All of the above claims are rejected.

Reconsideration of the rejection of this application is respectfully requested in view of the above amendments and the following remarks.

Amendments to Claims

Claims 37 and 72 have been amended so that after the starting daily dosage (250 mg/1.25 mg) the daily dosage range for metformin is -- up to about 750 mg --. In Claim 72, the maximum amount of glyburide (after the staring dosage) is 15 mg.

Since the starting dosage for metformin in Claims 37 and 72 is defined as 250 mg metformin, then the lower portion of the daily range of 160 to 750 mg is no longer applicable since it must now be a minimum of 250 mg per day.

Likewise, the daily dosage range for glyburide has been changed "from about 0.5 to about 15 mg" to up to 15 mg per day since the starting dosage for glyburide is 1.25 mg and thus cannot be 0.5 mg per day.

Claims 37 and 72 have been amended to define the weight ratio of metformin to glyburide of about 200:1 as set out in Claim 47 (now cancelled).

Claims 46 and 47 have been cancelled.

Claim Rejections - 35 U.S.C. §112

Claims 37, 45 to 48, 53, 54, 72, 75 to 78 and 80 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner contends that:

> "Independent claims 37 and 72 recite 'wherein the starting daily dosage is 250mg metformin and 1.25mg glyburide'. The total amounts of drug combination provided as a starting dose per day must be equal to 250 mg metformin and 1.25 mg glyburide. In other words, it cannot be go over the amount of 250 mg metformin and 1.25 mg glyburide during the first day of the treatment. However, the recitation of

'wherein the metformin in said low dose combination is administered in a daily dosage in an amount within the range from about 160 mg to about 750mg...' in claim 37 and 'the metformin in said low dose combination is administered in a daily dosage of at most about 750 mg' in claim 72 leave the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear.

Similarly, the recitation of 'the metformin in said low dose combination is administered in an amount within the range from about 160 to about 750 mg....' in claim 48, 'the combination of metformin and glyburide in said low dose combination comprises a 250 mg metformin/1.25 mg....once a day or twice a day' in claim 53 and 'the 250 mg metformin/1.25 mg glyburide dosage...twice daily...' in claim 54 renders the definition of the subject-matter of said claims unclear.

For the examination purpose, the term 'the starting daily dosage is 250mg metformin and 1.25mg glyburide' is construed as 'the treatment is initiated at 250 mg metformin and 1.25 glyburide dose'."

Claim 37 has been amended to make it clear that in accordance with Applicant's invention, metformin and glyburide are administered in a starting daily dosage of 250 mg metformin and 1.25 mg glyburide and after the starting daily dosage the daily dosage of metformin being up to about 750 mg per day and the daily dosage of glyburide being up to about 15 mg per day.

Claim 72 has been amended in a similar manner.

It is submitted that it is clear from the amended claims that the starting daily dosage for metformin is 250 mg and thereafter up to a daily maximum of 750 mg per day and the starting daily dosage of glyburide is 1.25 mg glyburide and thereafter up to a maximum of 15 mg per day.

In view of the above amendments, it is submitted that Claims 37, 45, 48, 53 to 54, 72, 75 to 78 and 80 are in compliance with 35 U.S.C. §112, second paragraph.

Discussion of Invention

Applicant's invention as claimed is defined as a method for

1) first line treatment of diabetes

2) in a drug naïve patient

3) wherein a low dose of a combination of metformin and glyburide (starting dose of 250 mg metformin and 1.25 mg glyburide) in a weight ratio of 200:1 is administered

4) so that daily dosage of metformin is 750 mg or less, and

5) where the glyburide has a special particle size distribution of at most 25% of the particles are less than 11 μm and at most 25% are greater than 46 μm.

The essence of Applicant's method is to employ a maximum daily dosage of 750 mg metformin together with the glyburide of special particle size distribution in a weight ratio of metformin:glyburide of about 200:1, to achieve equivalent efficacy as compared to efficacy achieved with prior art dosing that is more than 800 mg metformin/day, but with reduced side effects as compared to that observed with such prior art dosing. See page 41, lines 5 to 35 of the Specification.

In Applicant's method as claimed, use of the combination of the low dose formulation of metformin and glyburide (200:1 weight ratio) in first line therapy (at most 750 mg/day metformin) is safer (less side effects) than the use of higher doses (greater than 800 mg/day metformin), without substantial loss in efficacy. Applicant's invention as claimed resides in use of the low dose formulation of 250 mg metformin / 1.25 mg glyburide to provide less than (or at most) 750 mg/day of metformin, in first line therapy, and which has essentially the same efficacy as the formulation containing 500 mg metformin / 2.5 mg glyburide which provides more than 800 mg/day, but use of the low dose formulation results in reduced side effects. Please note Figures 9 and 10 which show that use of the combination of 250 mg metformin / 1.25 mg glyburide results in substantially reduced side effects as compared to use of 500 mg metformin / 1.25 mg glyburide. See Figures 1 to 8 wherein it is shown that the use of low dose of 250 mg metformin / 1.25 mg glyburide provides essentially the same efficacy as use of the dose of 500 mg metformin / 2.5 mg glyburide. As will be seen hereafter, with regard to Figures 1 to 10, where the low dose metformin (250 mg) of the invention is used, the daily amount of metformin is less than (or at most) 750 mg while where the high dose of metformin (500 mg) is used, the daily amount of metformin is greater than 800 mg (prior art). This clearly demonstrates that Applicant's method as claimed which employs a low dose formulation to provide a daily dosage of metformin of at most 750 mg is patentable over methods of treating diabetes with higher doses of metformin in combination with glyburide.

Please note page 11 of the Specification starting at line 34 and continuing to page 12, line 20:

> "In carrying out the method of the invention employing the preferred starting low dose pharmaceutical formulation containing metformin and glyburide, to treat drug naive patients for diabetes, the efficacy in treating drug naive patients is at least substantially equivalent and incidence of side effects (gastrointestinal side effects and hypoglycemia) is surprisingly significantly and substantially reduced as compared to

patients on higher daily dosages of metformin and glyburide (that is in starting dosages prescribed in generally accepted medical practice for treating diabetes). Thus, while efficacy in treating drug naive patients as measured by decrease in hemoglobin A_{1c} (HbA_{1c}) from baseline over time, decrease in fasting plasma glucose (FPG), increase in post-prandial insulin levels, and decrease in post-prandial glucose (PPG) excursion, are essentially substantially equivalent in the above-described patients when employing the low dose pharmaceutical formulation employed herein and substantially higher daily dosages, incidence of hypoglycemia and gastrointestinal side effects in drug naive patients treated with substantially higher daily dosages are substantially greater than in patients treated with the low dose pharmaceutical formulation."

It is submitted that Applicant's method as claimed is patentable over the combination of the cited Barelli et al. patent, Ohmura et al., *Drug Facts and Comparisons*, and Bauer et al. patent.

Claim Rejections - 35 U.S.C. §103

Claims 37, 45 to 48, 53, 54, 72, 75 to 78 and 80 are rejected under 35 U.S.C. §103(a) as being unpatentable over Barelli et al. (WO 97/17975, pub. date: May 22, 1997, equivalent to US Patent 5,922,769) in view of Ohmura et al., *Drug Facts and Comparisons*, and Bauer et al. (US Patent 5,258,185, issue date: Nov. 2, 1993).

The Examiner contends that:

"The claims are directed to a method of treating type 2 diabetes comprising administering to a drug naive human patient, as first line therapy, a low dose of a combination of metformin and glyburide where the daily dosage of metformin is 250mg; the daily dosage of glyburide is 1.25mg. Further limitations include: metformin and glyburide is formulated as a single dosage form (claim 45); weight ratio of metformin and glyburide is from about 400:1 to about 50:1 (claim 46); and that the glyburide having particular particle distributions and the patient population being drug naive patients as recited in the claims.

Barelli et al. teach a combination of metformin and glibenclamide (glibenclamide and glyburide are synonymous), in a weight ratio higher than 1:100, being useful for the treatment of type II diabetes (claims) and that the combination makes the therapeutical effect optimum at any time of the progression of the disease, starting from the onset of the disease in NID diabetics (column 3, lines 19-20 and 49-50). Barelli et al. also disclose that the weight ratio of metformin and glibenclamide is 200:1 (column 2, lines 18-20) which overlaps with the claimed weight ratio; that said combination of dosages can be used starting from the onset of the disease in NID diabetics as long as the ratio of (higher than) 1:100 ratio between the two active principles is maintained, in both the multiple and submultiple dosages (column 3, lines 49-52 and 59-62); that 'when the tablets are subdivided, thus obtaining minor

and/or fractional daily dosages, the fixed ratio, which is the balanced...' (column 3, lines 52-55); that 'the therapeutic rationale of said studies suggested the use of combined formulations of medicaments capable of finding a remedy for both the deficiency in insulin secretion and the insulin-resistance condition' (column 1, lines 48-55); and that 'the combined therapy (sulfonylurea+biguanide) palys therefore a specifically important therapeutical role, since it allows to obtain an effective metabolic control in those patients with diabetes of type II, in which the therapy with only sulfonylureas or only biguanides becomes ineffective with time' (column 1, lines 62-67). Barelli et al. further teach a single coated tablet in EXAMPLE 1 (column 9, lines 25-26) which contains 500 mg metformin and 5 mg glibenclamide.

Ohmura et al. teaches the efficacy of low-dose metformin alone or combination of sulfonylurea (e.g., glibenclaimide) in the treatment of type 2 diabetes mellitus, wherein metformin is started at 250mg dose and titrated up to 750mg daily (pages 890-891 and 894).

Facts and Comparisons is being supplied as a supplemental reference to demonstrate the state of art knowledge in using 1.25 mg glyburide as a known antidiabetic agent (for patient who may be more sensitive to hypoglycemic drugs).

Bauer et al. teaches pharmaceutical formulations of glibenclamide rapidly releasing the active substance for the treatment of diabetes (see abstract). Bauer et al. disclose improved drug release and bioavailability (column 2, lines 17-22) of the drug glibenclamide by using a preparation having micronized glibenclamide with mean particle size of ± 5 μm which overlaps with the instantly claimed particle size of 2- 60 μm.

The difference between Barelli et al.'s teaching and the instant claimed invention lies in that Barelli et al. do not explicitly teach (i) the patient population being drug naive patients or the first line treatment of diabetes, (ii) a low dose of a combination of 250mg and 1.25mg glyburide as starting dosage, (iii) so that daily dosage of metformin is 750mg or less, and (iv) glyburide having particular particle distributions."

The Examiner further contends that:

"With regard to the patient population, although Barelli et al. do not explicitly teach that the combination is administered to a drug naive patient as a first line therapy, Barelli et al. do disclose that the combination teaches a therapeutic effect for treating type 2 diabetes, optimum at any time of the progression of the disease, starting from the onset of the disease in NID diabetics. Since the patient population of Barelli et al.'s method of treatment is type 2 diabetic, without identifying a patient's drug status and treatment history, one having ordinary skill in the art still would have been motivated to treat a drug naïve patient with Barelli et al.'s combination of metformin and glyburide as a first line therapy. Therefore, it would have been obvious to someone of ordinary skill in the art at the time of the instant

invention to practice the treatment of Barelli et al. in view of Bauer et al. to result in the practice of the instant invention with a reasonable expectation of success.

With respect to the recitation of metformin dosage being 250 mg and glyburide dosage being 1.25 mg, although Barelli et al. do not explicitly teach this particular dosage, Barelli et al. have provided guidance that 1500mg metformin and 15 mg glyburide are the maximum recommended daily dosage in the combination (column 3, lines 37-40) with recommended weight ratio of greater than 100:1, particularly 200:1 (column 2, line 20) between metformin and glyburide. Furthermore, Barelli et al. teaches that the tablets can be 'subdivided, thus obtaining minor and/or fractional daily dosages, the fixed ratio, which is the balanced...'. Thus, one having ordinary skill would have expected as taught by Ohmura et al. (Current Therapeutic Research, Vol. 59, No. 12, December 1998, pp. 889-895) and Drug Facts and Comparisons (1995 Edition, pp. 547) that initiating therapy with 250 mg metformin and 1.25 mg glyburide would be useful for the treatment of type 2 diabetes mellitus patient, especially for patients who are more sensitive to hypolgycemic drugs...."

"With respect to the specific particle distribution of glyburide, Bauer et al. teaches pharmaceutical formulations of glibenclamide rapidly releasing the active substance for the treatment of diabetes (see abstract). Bauer et al. disclose improved drug release and bioavailability (column 2, lines 17-22) of the drug glibenclamide by using a preparation having micronized glibenclamide with mean particle size of ± 5 μm which overlaps with the instantly claimed particle size of 2- 60 μm. Therefore, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to prepare micronized glibenclamide for the combination of metformin and glibenclamide as disclosed by Barelli et al. in view of Bauer et al. to result in the drug combination of the instant invention, motivated by Bauer et al. that glibenclamide is virtually water-insoluble (column 2, line 9) and micronized glibenclamide improves its solubility and bioavailability (column 2, lines 31-32). Although the prior art does not discloses the instant 'at most 25% of the particles are less than 11 μm and at most 25% are greater than 46 μm'. However, one having ordinary skill in the art would have expected at the time of the invention was made that the specific particle distribution percentage of the instant claims would have been characteristic of the modified prior art method. Generally, differences in a particle distribution percentage or concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such particle distribution concentration is critical. Where the general conditions of a claim are disclosed in the prior art, it not inventive to discover the optimum or workable particle distribution percentage or concentration by routine experimentation.

With respect to the recitation of claim 54 regarding patient baseline measurements, those values are the same as those measured for the type 2 diabetic patient as disclosed by Barelli et al. (column 4, lines 23-29).

With respect to the recitation of 'lowering blood glucose in a hyperglycemic human patient, decreasing insulin resistance, decreasing hemoglobinAlc, increasing post-prandial insulin levels or decreasing prandial glucose excursion' in claim 72, since the drug combination of metformin and glyburide is the same as what's disclosed in the prior art and are being administered to the same patient population, the recited effects are expected and thus do not limit the claims.

Although the instant claims use the different names for the said ingredients than those taught in the cited references, these references are particularly pertinent and relevant because all the claimed species and their roles are well taught in the cited reference. Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a)."

It is submitted that Applicant's invention as claimed is patentable over Barelli et al.

Barelli et al. disclose tablets containing a combination of 500 mg metformin and 5 mg glyburide for treating diabetes, so as to allow a daily dosage of 1500 mg metformin and 15 mg glyburide (column 2, lines 64 to 67), for maximum benefit, although such tablets may be subdivided. The Barelli et al. combination is 500 mg metformin / 5 mg glibenclamide or a 100:1 ratio to achieve good efficacy with minimal side effects.

Barelli et al. teach using a metformin:glyburide weight ratio of 100:1, whereas Applicant requires a ratio of 200:1.

Barelli et al. in Column 2 starting at line 16 continuing to line 41 teach that use of metformin in a weight ratio to glyburide of 200:1 results in a "quantitative unbalance of the medicaments in combination". Therefore, Barelli et al. use a ratio of 100:1. Thus, Barelli et al. teach away from use of Applicant's weight ratio of its low dose combination of metformin:glyburide of 200:1.

Barelli et al. has nothing to do with Applicant's inventive concept as claimed.

1) Applicant's method requires treating with a low dose combination of metformin (a maximum 750 mg daily) and glyburide.

Barelli et al. does not disclose or suggest using a low dose of metformin but teach using a daily dose of up to 1500 mg metformin. Until Applicant's invention, no one used a low dose of metformin, that is a maximum of 750 mg daily for treatment of diabetes. It therefore has to be presumed that Barelli et al. is not implicitly or otherwise suggesting to use a low dose of metformin, that is 750 mg or less, but apparently is suggesting to use more than 750 mg/day up to 1500 mg/day.

2) Barelli et al. makes no mention of particle size distribution of glyburide. Applicant's method requires a specific particle size distribution of glyburide not disclosed or suggested in Barelli et al.

3) Barelli et al. uses a weight ratio of metformin:glyburide of 100:1 and teaches that using a weight ratio of 200:1 (as does Applicant) is undesirable.

In the clinical study described in Columns 6 and 7 of Barelli et al., the patients treated were not drug naïve but were previously treated with combinations of metformin and glyburide as indicated at Column 7, lines 28 to 34.

Applicant has shown in working Example 3 that in accordance with the present invention use of a combination of 250 mg metformin and 1.25 mg glyburide to provide a metformin daily dose of less than 750 mg has reduced side effects and substantially equivalent efficacy as compared to a Barelli et al. combination of 500 mg metformin and 2.5 mg glyburide to provide a metformin daily dose of more than 800 mg. The fact that, in accordance with the present invention, use of a low dose combination of 250 mg metformin and 1.25 mg glyburide to provide a maximum daily dosage of 750 mg metformin has substantially equivalent efficacy of a Barelli et al.-like combination which provides a daily dosage of greater than 800 mg metformin, while causing reduced side effects as compared to the Barelli et al.-like combination is, indeed, surprising and unexpected.

As seen in Example 3, Applicant has compared efficacy and safety of a combination of 250 mg metformin / 1.25 mg glyburide to provide at most 750 mg metformin/day versus efficacy and safety of a combination of 500 mg metformin / 2.5 mg glyburide to provide more than 800 mg metformin per day. The glyburide used in both compositions is the specially sized glyburide as claimed which is not disclosed or suggested by Barelli et al. The key to the invention is use of the combination to provide at most 750 mg metformin per day. The results obtained, namely reduced side effects and substantially equivalent efficacy, is indeed surprising and unexpected. It is indeed unobvious that using a combination to provide less metformin (less than 750 mg/day) would provide substantially equivalent efficacy but reduced side effects as compared to using a combination to provide more metformin (greater than 800 mg/day). This is surprising and unexpected.

See pages 36 and 37 (Example 3) of the Specification wherein it is stated as follows:

"**RESULTS**

The results obtained from the above studies indicate that the low dose metformin-glyburide (250/1.25) formulation of the invention achieved glycemic control at least essentially equivalent to the high dose metformin-glyburide (500/2.5) formulation as evidenced by

(1) a therapeutic response for hemoglobin A1c, namely, a reduction in HbA1c of below 7% (from a mean baseline of 8.2%) at week 20 (Figures 1, 2 and 3), at weeks 20 and 32 and final visit (Figures 4 and 5)

(2) a therapeutic response for fasting plasma glucose (FPG), namely, a reduction in FPG to less than 126 mg/dL after 20 weeks (from a baseline of about 175 mg/dL), (as shown in Figures 6)

(3) a therapeutic response for post-prandial insulin levels, namely an increase in post-prandial insulin of 19-25 μiu/mL (microinternational units/mL) (Figure 7)

(4) a therapeutic response for post-prandial glucose excursion (PPG) (that is the difference between post-prandial glucose and fast plasma glucose), namely, a decrease in post-prandial glucose excursion at week 20 of 17.7 for the 500/2.5 mg combo and 20.8 for the 250/1.25 mg combo versus 15.2 for metformin, 6.8 for glyburide. (Figures 8A and 8B).

At the same time, the above efficacy results employing the low dose formulation of the invention (Example 1) were achieved with reduced incidence of side effects (Figures 9 and 10).

As seen in Figure 9, the incidence of hypoglycemia employing the low dose formulation of the invention (Example 1) is less than about 1/3 of that occurring using the prior art high dose formulation (Example 2) employed in generally accepted medical practice for treating diabetes.

As seen in Figure 10, the incidence of gastrointestinal side effects employing the low dose formulation of the invention (Example 1) is less than 20% of that occurring using the high dose formulation (Example 2) employed in generally accepted medical practice for treating diabetes.

A discussion of the above results follows."

See pages 38 and 39 (Example 3) of the Specification wherein it is stated as follows:

> "As first line therapy, a single formulation of fixed combination metformin/glyburide in ratio of a 200:1 metformin/glyburide was evaluated using two different dose strengths, a low dose (metformin/glyburide 250/1.25 mg) and a medium dose (metformin/glyburide 500/2.5 mg). The two dose strengths of fixed combination metformin/glyburide product were compared in a double-blind study to placebo, glyburide monotherapy and metformin monotherapy. Mean final doses achieved in each treatment arm were approximately 5.3 mg of glyburide [glyburide alone], 1307 mg of metformin [metformin alone], 557/2.78 mg [daily] of low dose (250/1.25 mg) metformin/glyburide fixed combination and 818/4.1 mg [daily] of medium dose (500/2.5 mg) fixed combination. When used as first line therapy, fixed combination metformin/glyburide treatment achieved statistically significant improvement in glycemic control compared to metformin, glyburide or placebo. The interim open-label treatment data confirmed the clinical utility of fixed combination therapy in a more 'glycemically diverse' patient population and for a longer period of time."

Thus, Applicant has presented comparative data which compares the formulation of the invention versus the closest prior art formulation.

In view of the above, it is quite clear that Applicant's method as claimed is neither disclosed nor suggested by Barelli et al. and thus is patentable over Barelli et al.

The Examiner cited Ohmura et al. which was published in December, 1998.

As will be seen in the file wrapper of the present application, Applicant submitted a Declaration of Prior Invention which was filed on or about February 3, 2003 which established reduction to practice of the present invention prior to July 15, 1998, that is prior to the effective date as a reference of Ohmura et al., thereby removing Ohmura et al. as a reference against the subject application. Thus, Ohmura et al. is no longer applicable as a reference against the invention as claimed herein.

It is submitted that Applicant's invention is claimed as patentable over the *Drug Facts and Comparisons* reference.

The *Drug Facts and Comparisons* reference discloses doses of glyburide of 1.25 mg to 20 mg. However, there is no disclosure or suggestion to references of combinations of glyburide and metformin.

It is submitted that Applicant's invention is claimed as patentable over Bauer et al.

U.S. Patent No. 5,258,185 to Bauer et al. discloses in Col. 2, lines 17 to 20,

> "microionized, i.e. finely comminuted, glibenclamide (mean particle size ±5 μm) showed an improved drug release and bioavailability above all in the presence of tensides . . ."

There is no disclosure or suggestion in Bauer et al. of a method of treating diabetes in a drug naïve patient employing a low dose of a combination of metformin and glyburide. Bauer et al. discloses formulations containing glyburide but not metformin. In addition, the glyburide employed in Applicant's invention as claimed will have a mean particle size greater than ±5 μm.

Applicant's claim in Claims 37 and 72 glyburide having a particle size distribution so that at most 25% is less than 11 μm which means that at least 75% is greater than 11 μm. Claims 75 to 78 depend from Claim 37. Thus, all of the claims define a particle size range for glyburide of greater than ±5 μm. Accordingly, it is clear that Applicant's invention as claimed is patentable over Bauer et al.

Applicant's method as claimed is also patentable over a combination of Barelli et al., *Drug Facts and Comparisons*, and Bauer et al. As indicated, Barelli et al. does not disclose or suggest use of low dose metformin (160 to 750 mg daily). Barelli et al. is devoid of Applicant's inventive concept of use of a combination of low dose metformin (maximum daily dosage of 750 mg) and specially size glyburide employing a 200:1 weight ratio of metformin:glyburide. Even if Barelli et al. is taken with *Drug Facts and Comparisons*, Bauer et al. so that the Barelli et al. combination includes the Bauer et al. sized glyburide (which is different from Applicant's), the resulting combination would not make Applicant's method obvious since none of the references taken alone or in combination discloses or suggests use of low dose metformin (at most 750 mg/day) or treatment of drug naïve patients in first line therapy or use of specifically sized glyburide having a mean particle size of greater than ±5 μm in the 200:1 weight ratio which low dose combination is as efficacious as prior art higher dose combinations for treating diabetes but which causes reduced side effects as compared to prior art higher dose combinations.

In view of the foregoing, it is submitted that Claims 37, 45, 48, 53, 54 and 75 to 78 and 80 overcome all formal objections and are patentable over all cited art taken in any combination and therefore are in condition for allowance.

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000

Burton Rodney
Attorney for Applicant
Reg. No. 22,076
Phone: 609-252-4336
Date: July 3, 2008